TO: HHS
FROM: M. Louise Markert MDPhD
RE: Subpart D Panel Review of UCLA IRB #01-11-064, Dr. Paul Krogstad MD
DATE: July 1, 2003

The PI would like to study the biology of the thymus in HIV infection in adolescents. The effect of long term exposure of HIV on thymic function is unknown. The PI hypothesizes that prolonged and poorly controlled HIV infection will correlate with thymic senescence. The scientific merit of this application is outstanding.

The research subjects

The PI proposes to study three groups of research subjects, i) adolescents/young adults (13-21 years old) with perinatal HIV infection (PI-A), ii) age-matched seronegative control subjects (SN-A), and adolescents with HIV infection acquired via recent adult behaviors (AB-A). They hope to enroll 20 SN-A, 20 AB-A, and up to 60 PA-A between the CHLA and UCLA clinics. The seropositive subjects will be stratified by viral load.

The specific aims

The first specific aim will compare parameters of thymopoiesis and T cell turnover in the three populations. The studies to accomplish this are the following:

i. Measurement of T cell receptor rearrangement excision circles (TRECs) on blood samples. The subjects will be seen at 0, 6, 12, and 18 months.

ii. Flow cytometry assessment of naive T cells on blood samples on the same time frame as in "i".

iii. Volumetric imaging of the thymus by chest CT. This will be done once in all subjects. Some HIV-seropositive subjects may receive a second CT at 18 months if the immune parameters change dramatically.

iv. In vivo metabolic labeling using nonisotopic labeled glucose infusions and blood sampling. This involves an overnight admission to the General Clinical Research Center (GCRC) and 2 additional clinic visits. The subjects will be given infusions of 5-10% labeled glucose over 24 hours with a dose of 2 grams/kg. The certificate of analysis was presented. This will be done in 15 SN-A, 10 PI-A and 10 AB-A.

The second specific aim will assess viral factors. Virus will be isolated from the PI-A and AB-A subjects and drug resistance and nef gene mutations will be sought by sequencing. This study involves blood draws. This will be done in 10 PI-A and 5-10 AB-A.

The third specific aim will assess cellular immune responses of the research subjects. In particular the cytotoxic lymphocyte responses to Candida, Epstein Barr Virus and influenza will be assessed. Lymphoproliferative, ELISPOT (done in 20 PI-A and 20 AB-A who have < 400 copies/ml for 1 year with 5-10 SN-A controls) and V-beta repertoire analysis will be done. This will involve blood draws. The blood draws are 50-60 cc for these tests.

Study portion under consideration regarding Subpart D

The Subpart D review panel was asked to review the use of deuterium labeled glucose in

adolescents. This reviewer does not feel that this procedure has risk above minimal risk. This infusion has no radioactivity. The infusion carries an amount of glucose that is safely tolerated. The overnight stay in the GCRC will be an appropriate environment with skilled medical staff to insure safety. In my opinion this research is categorized as 46.404 - "Research not involving gretaer than minimal risk". As an aside, the seronegative adolescents have volunteered for this study to help advance understanding of HIV. They should be allowed to participate.

I would like to comment on the CT scans in the seropositive and seronegative research subjects. I feel that the CT scans in the seropositive subjects are above minimal risk because of the radiation exposure. They carry no prospect of direct benefit to individual subjects but are likely to yield generalizable knowledge about the subjects' disorder or condition. These examinations fall under 46.406.

The CT scans in the seronegative subjects are above minimal risk but cannot yield knowledge about the subjects condition, because the seronegative subjects don't have a condition. I feel that the studies present an opportunity to understand a serious problem affected the health or welfare of children (HIV infection) and thus fall under 46. 407. The information to be gained in this study will enhance our understanding of HIV pathogenesis, and, possibly in the future, improve the treatment of HIV infection.

I approve this protocol with the stipulation that the informed consent document be changed to indicate that a CT scan is associated with more radiation exposure than a chest X-ray.